

REMARKS

The title has been amended to be consistent with the Declaration.

In response to the above Office Action, claim 1 has been amended to recite that the organic solvent is a water-immiscible organic solvent. Support for this can be found in dependent claim 5. In addition, claim 1 has been amended to limit the method to steps (d-1)-i) and (d-1)-ii). This specific method was claimed in dependent claim 17. As a result, claims 5, 8-10, 17, and 18 have been cancelled.

A Request for Continued Examination is being filed with this Reply to enable the Examiner to consider the amended claims.

In the Office Action, the Examiner rejected claims 1-7, 15, 16, 18-20, and 22 under 35 U.S.C. §102(b) for being anticipated by U.S. Patent No. 6,270,802 to Thanoo et al., hereafter Thanoo. Now that claim 1 has been limited to the method of claim 17, which claim was not included in this rejection, it is submitted this rejection is now moot. Its withdrawal as a ground of rejection of the claims is requested.

The Examiner also rejected claims 8-14, 17, and 21 under 35 U.S.C. §103(a) for being obvious over Thanoo. Of these claims, claims 8, 9, and 10 have been cancelled.

As defined in amended claim 1, the present invention relates to a method for the preparation of microspheres which comprises the following circulation steps:

- (a) emulsifying a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and a water-immiscible organic solvent having a boiling point lower than that of water into an aqueous solution in an emulsifying device to form an emulsion wherein said medicament-containing polymer solution is dispersed in the aqueous solution;
- (b) transferring the obtained emulsion into a microsphere storage tank;

(c) introducing a part of the emulsion from the microsphere storage tank into a cross flow filter;

(d-1)-i) returning a liquid passing over the cross flow filter to the microsphere storage tank;

(d-1)-ii) recycling a filtrate filtered from the above cross flow filter as an aqueous solution for step (a), repeating steps (a) to (d-1), and evaporating said water-immiscible organic solvent in the microsphere storage tank during this circulation process and;

(e) collecting microspheres in the microsphere storage tank after step (d-1) is completed.

According to the method of the present invention, the aqueous solution can only effectively be separated from the emulsion prepared in the emulsifying device and transferred into the microsphere storage tank by means of the cross flow filter. Hence, even if the emulsion producing process is repeated, the emulsion in the microsphere storage tank can be kept at a constant volume without increasing. Accordingly, this process permits downsizing of the apparatus, and further since the filtrate is used as the aqueous solution in the emulsifying step, the process can be made airtight including the emulsifying step. This makes it effective for inhibiting bacterial contamination.

Moreover, according to the method of the present invention, the emulsification and the evaporation of the water-immiscible organic solvent can be done in parallel. Hence the production of microspheres can be done with a high efficiency.

In addition, according to the present method, even when a large amount of microspheres are produced, the emulsifying scale at one time can be made small, and

hence, homogeneous emulsification can easily be done resulting in microspheres of high quality. Even in a single apparatus for producing microspheres, the microsphere production scale at one time can be easily controlled by varying the emulsifying frequency.

Thanoo relates to a method for formulating a plurality of active agent containing polymer bodies. This method comprises:

- a) providing a suspension of active agent containing polymer bodies in a continuous phase in a process vessel;
- b) while maintaining the polymer bodies in suspension, replacing the continuous phase with a formulating medium by moving the suspension through a filter adapted to remove the continuous phase and return the polymer bodies as a suspension to a process vessel; and
- c) removing the suspension of active agent containing polymer bodies and formulating medium from the process vessel.

The polymer bodies in Thanoo include microspheres (cf. col. 1, lines 53-56 and col. 2, lines 37-40). In addition, the term “formulating” in Thanoo means formulating the microspheres into a final product, (cf. col. 1, lines 48-50 and col. 2, lines 45-49); not making the microspheres.

Thus, the invention of Thanoo is a formulation process of previously prepared microspheres or the like, where a filter is used in the formulation step.

It is noted that Thanoo also describes, as set forth, for example in claims 16 and 19, a method of both making agent containing polymer bodies and formulating the agent containing polymer bodies. Here steps a) to e) are for producing the active agent

containing polymer bodies, and step f) for formulating the active agent containing polymer bodies thus prepared (i.e., steps a) to e) above. While a filter is used in step f) where the polymer bodies are formulated, no filter is used in steps a) to e) where the polymer bodies are made. The material used in steps a) to e) to make the active agent containing polymer bodies by removing the solvent is in the form of an emulsion, which is to be distinguished from the suspension used and filtered to formulate the active agent containing polymer bodies. It appears the Examiner may be confusing this emulsion of the steps used to make the polymer bodies in Thanoo with the suspension of the steps used to formulate the already prepared polymer bodies into a final product because it is the suspension of the bodies that is subjected to filtration, not the emulsion used to make them.

The Examiner points out on page 7 of the Office Action that Thanoo discloses that polymer bodies transferred from the source 10 to the holding tank 24 may not yet be solidified or may still be in the process of forming (col. 5, lines 37-39 of Thanoo) and, therefore, that “some of the polymer bodies in the suspension may not be solidified, or otherwise still may be in the process of forming” when they are subjected to filtration, “thus meeting the claimed limitations.” However, holding tank 24 is separate from formulating vessel 16, and it is the suspension in vessel 16 that is passed through a filter, not the suspension of the polymer bodies in holding tank 24. To speculate that the polymer bodies are still being formed when they are transferred from tank 24 to vessel 16 is pure conjecture on the part of the Examiner. There is nothing in the teachings of Thanoo that suggests that the bodies “may still be in the process of forming” when they are transferred to formulation vessel 16. Just because Thanoo

“does not explicitly disclose that 100% of the polymer bodies are solidified” when they are passed to formulation vessel 16, does not give the Examiner the right to argue they necessarily are not solidified.

In col. 5, lines 45-49 of Thanoo it is disclosed that the polymer bodies may be transferred to a process vessel that will serve as a solvent removal vessel as well as perform one or more of the concentrating, washing, and formulating steps. This passage merely means that one vessel may have a plurality of functions, but it does not mean that the removal of solvent is performed at the same time with the concentrating, washing, and formulating steps.

Thus Thanoo is a process for formulating already prepared active agent containing polymer bodies (e.g., microspheres or the like), and it is in this formulation process where a filter is used.

In contrast, in the present process the filter is used in the process of making the microspheres in the first place, and it is the emulsion used in this process that is subjected to filtration. In Thanoo in the comparable steps for making the microspheres (e.g., steps a) to d) of claim 16 or 19, the emulsion is not subjected to filtration.

The use of the filter in the formulation process of Thanoo is to a) replace the continuous phase of the suspension of the active agent containing polymer bodies with a formulating medium or b) replace the continuous phase in the suspension with water followed by replacing the water with a formulating medium. In the present invention, the filtrate obtained from the filter by passing the emulsion through it is recycled as an aqueous solution for use in the emulsification step. Thus, the use of a filter in the formulation process of Thanoo is quite different from the use of the cross flow filter in

the preparation of the microspheres in the present invention. Thanoo may teach the use of a solvent removal step in the process of making the microspheres, but the emulsion is never subjected to filtration or to any circulation process as claimed. Only the already prepared microspheres are subjected to a filtration and a circulation process.

In Example 2 of Thanoo, for example, where the vessel 316 serves as both a solvent removal vessel and a processing vessel for the concentrating and washing steps (column 10, lines 53-55), the suspension of the microspheres is passed through the hollow fiber filter 322 from which the continuous phase is removed via line 332 and the concentrated suspension is returned to the process vessel 316. Thus the filtrate here is being discarded.

In contrast, in the present invention, the filtrate of the filtration step is being recycled as an aqueous solution to the emulsion-producing step. This is a significant difference over Thanoo because Thanoo not only does not recycle any filtrate, the filtrate obtained in Thanoo is from a suspension of already prepared microspheres, not from an emulsion used to make the microspheres.

In general, for the preparation of microspheres, the ratio of the continuous phase (aqueous solution) to the oil phase (medicament-containing polymer solution) is a very important factor, and it is known that the smaller the ratio of the continuous phase, the lower the content of the medicament in the microspheres obtained. This is due to the extremely low solubility of the water-immiscible organic solvent (used in the oily phase) in the continuous phase, by which the solidification rate of the oily drops effects the ratio of oily phase/continuous phase. Owing to the effects, when the filtrate (including

water-immiscible organic solvent remaining) obtained by passing the emulsion through a cross flow filter is recycled as an aqueous solution to the emulsification step, there generally would be concern that it would result in a lowering of the quality of the microspheres.

Contrary to such concern, it has surprisingly been found that the filtrate can be recycled without lowering the quality of the product by carrying out simultaneously and in parallel the emulsification, the evaporation of organic solvent and the cross flow filtration during the circulation process.

In summary, Thanoo does not disclose 1) cross flow filtration of the emulsion in the step of producing microspheres, 2) the recycling of any filtrate let alone a filtrate as an aqueous solution to the emulsifying step, or 3) the carrying out in parallel of the evaporation of the water-immiscible organic solvent from the emulsion and the cross flow filtration of the emulsion. This results in the production of the high quality microspheres with a high efficiency.

As required by M.P.E.P. §2143, to establish a prima facie case of obviousness, it is necessary that all of the claimed features be shown or suggested in the prior art. Since Thanoo does not disclose or suggest at least any of the above three features of applicants' invention, as set forth in claim 1, it is submitted that neither this claim nor claims 2-4, 6, 7, 11-16, and 19-22 dependent therefrom can be considered obvious over this reference. Its withdrawal as a ground of rejection of the claims under §103(a) is therefore requested.

It is believed claims 1-4, 6, 7, 11-16, and 19-22 are in condition for allowance.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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